



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,134	09/14/2006	Irina Velikyan	PH0334	7198
36335 7590 06/28/2010 GE HEALTHCARE, INC. IP DEPARTMENT 101 CARNEGIE CENTER PRINCETON, NJ 08540-6231				
EXAMINER				
FERREIRA, MELISSA JEAN				
ART UNIT		PAPER NUMBER		
1618				
MAIL DATE		DELIVERY MODE		
06/28/2010		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/552,134

Applicant(s)

VELIKYAN ET AL.

Examiner

MELISSA PERREIRA

Art Unit

1618

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 May 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3.5 and 8-16 is/are pending in the application.
- 4a) Of the above claim(s) 16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3.5 and 8-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/GS/US)
Paper No(s)/Mail Date _____

- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Claims 1-3,5 and 8-16 are pending in the application. Claim 16 is withdrawn from consideration and claim 7 was canceled in the amendment filed 5/24/10.

Response to Arguments

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. Claims 1-3,5 and 8-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths et al. (WO03/059397) in view of Yngve (Int. Diss. Abs. **2001**, 62), Bottcher et al. (US 5,439,863) and Lidström et al. (*Tetrahedron* **2001**, 57, 9225-9283) and in further view of Maier-Borst et al. (GB 2056471A) and Wheaton et al. (*Industrial and Engineering Chemistry* **1951**, 43, 1088-1093) as stated in the office action mailed 2/22/10.

3. Applicant asserts that Bottcher does not teach of successfully applying microwave activation in coordination chemistry.

4. Bottcher teaches that the production of neutral transition metal complexes in a one-step process via the use of high energy input, such as ultrasound, microwave, laser beam, etc. with the advantage of short reaction time (i.e. a few minutes) and ease of separation of the formed complexes. Therefore, it would have been obvious to one

skilled in the art that any of the limited/finite choices of the high energy inputs are used to provide for the production of neutral transition metal complexes with the advantages of short reaction time (i.e. a few minutes) and ease of separation of the formed complexes. Further, all of the preferred embodiments do not need to be exemplified.

5. Also, Lidström et al. teaches that microwave technology has been used since the late 1970s for inorganic chemistry and 1980s for organic synthesis. The shorter reaction times are the main advantage of the microwave technique as microwave heating can be very rapid, producing heat profiles not easily accessible by other heating techniques. The microwave technique can provide 100 W and a metal-macrocyclic chelate complex may be generated via the microwave technique.

6. Since the microwave technique was known in the art to reduce reaction times of organometallic reactions, such as metal-chelate complexes, one would have a reasonable expectation of success for preparing radiotracer via labeling reactions with this improved microwave technique.

7. Applicant asserts that the examiner is effectively suggesting that a person skilled in the art would take a huge risk in combining Griffiths/Bottcher and not worry about the uncertainties and consequences. Lidström et al. alludes to the risks of microwave ovens: "This slow uptake of the technology has been principally attributed to its lack of controllability and reproducibility, safety aspects and a generally low understanding of the basics of microwave dielectric heating."

8. Lidström et al. recites, "In inorganic chemistry, microwave technology has been used since the late 1970s, while it has only been implemented in organic chemistry

since the mid-1980s. The development of the technology for organic chemistry has been rather slow compared, to for example, combinatorial chemistry and computational chemistry. This slow uptake of the technology has been principally attributed to its lack of controllability and reproducibility, safety aspects and a generally low degree of understanding of the basics of microwave dielectric heating. Since the mid-1990s, however, the number of publications has increased significantly (Fig. 1). The main reasons for this increase include the *availability of commercial microwave equipment* intended for organic chemistry and the development of the solvent-free technique, which *has improved the safety aspects*, but are mostly due to an increased interest in shorter reaction times.

9. Applicant asserts that Lidström et al. states: "The lack of control in domestic microwave ovens when performing assisted synthesis has led to a vast number of incidents, including explosions, being reported."

10. Lidström et al. recites, "The lack of control in domestic microwave ovens when performing microwave assisted synthesis has led to a vast number of incidents, including explosions, being reported." This statement is in regards to domestic microwave ovens while Lidström et al. further teaches that in the 1990s there has been a significant increase in the publications about microwave technology due to the increased availability of commercial microwave equipment which improved the safety aspects (Lidström et al. p9226, left column, first full paragraph).

11. Applicant asserts that there is substantial doubt as to whether what Bottcher applies on the kilogramme scale could be successfully translated to the microgramme

scale — i.e. at several orders of magnitude lower concentration. In the real world, the person skilled in the art would face those issues so applicants contend that the lack of evidence of success in Bottcher is (and must be) material to the argument. The scale of Bottcher is incompatible with that of both Griffiths and Yngve (because it is incompatible with radiopharmaceuticals in general).

12. The instant claims do not recite amounts/concentrations of the reagents. The reference of Bottcher et al. was not used to teach of the amounts/concentrations of the reagents for the synthesis of the metal complexes of the disclosure but was used to teach that microwave irradiation was known at the time of the instant invention for the preparation of metal complex salts for its advantages, such as continuous conversion, single-stage reaction with short reaction time and ease of separation of the formed complexes.

13. The reference of Lidström et al. was also used to teach of that microwave irradiation was known at the time of the instant invention for organometallic synthesis for its advantage of reduced reaction times.

14. Since the microwave technique was known in the art to reduce reaction times of organometallic reactions, such as metal-chelate complexes, one would have a reasonable expectation of success for preparing radiotracer, such as those of Griffiths and Yngve via labeling reactions with this improved microwave technique for the advantage of reduced reaction times due to the half-lives of radioisotopes.

15. Applicant asserts that the reaction reference to in Lidström et al. refers to a microwave reaction without solvent. A copy of the reference is provided – Shaabani [J.

Chem. Res., 672-673 (1998)]. It refers to a microwave reaction without solvent. The person skilled in the art would know that such a reaction is not suitable for the process of present claim 1. Hence, the combination Griffiths/ Lidström et al. or Yngve/ Lidström et al. does not lead to subject matter within the scope of present claim 1, since it teaches toward solvent-free reactions outside the scope of the present claims.

16. The reference of Shaabani [J. Chem. Res., 672-673 (1998)] was not found in PAIR.

17. The reference of Lidström et al. was not used to explicitly teach of solvent reaction conditions for the microwave technique but was used to teach that microwave technology has been used since the late 1970s for inorganic chemistry and 1980s for organic synthesis. The shorter reaction times are the main advantage of the microwave technique as microwave heating can be very rapid, producing heat profiles not easily accessible by other heating techniques. The microwave technique can provide 100 W and a metal-macrocyclic chelate complex may be generated via the microwave technique. Lidström et al. further teaches that in the 1990s there has been a significant increase in the publications about microwave technology due to the increased availability of commercial microwave equipment which improved the safety aspects.

18. Bottcher teaches of the production of neutral transition metal complexes in a one-step process combining metal ions with multitoothed chelating ligands via microwave irradiation in an aqueous medium (Bottcher column 2, lines 25-34).

19. Griffiths et al. teaches that the method of producing a radiolabeled gallium complex involves reacting the solution (i.e. pH-neutral buffer) of a peptide labeled

macrocyclic chelate with the ^{68}Ga diluted (dilute acid) from the $^{68}\text{Ge}/^{68}\text{Ga}$ titanium dioxide generator which can be fitted with an anion-exchange membrane. Therefore the reaction takes place in a solvent (i.e. aqueous) at 45°C for 30 minutes.

20. Therefore, it would have been obvious to one ordinarily skilled in the art to utilize the microwave technique of Bottcher and/or Lidström et al. for the method of producing radiolabeled gallium complexes for the advantage of minimizing the reaction time from 30 minutes to a few minutes as taught by Bottcher.

21. Applicant asserts that the chelator template synthesis of Lidström et al. is completely different from the subject matter of the present invention, wherein a pre-formed/pre-existing macrocyclic chelate is linked to a "targeting vector" and the radiogallium metal complex is formed from the same conjugated chelator. Hence, when the teaching of Lidström et al. is properly focused on what the reference itself actually teaches, Lidström et al. is silent on the use of microwave radiation to facilitate a reaction of the type: [macrocyclic chelate] + [metal] \rightarrow [metal complex of said macrocyclic chelator]

22. The reference of Lidström et al. was not used to explicitly teach of the reaction of [macrocyclic chelate] + [metal] but was used teach that microwave technology has been used since the late 1970s for inorganic chemistry and 1980s for organic synthesis. The shorter reaction times are the main advantage of the microwave technique as microwave heating can be very rapid, producing heat profiles not easily accessible by other heating techniques. The microwave technique can provide 100 W and a metal-macrocyclic chelate complex may be generated via the microwave technique. Lidström et al. further teaches that in the 1990s there has been a significant increase in the

publications about microwave technology due to the increased availability of commercial microwave equipment which improved the safety aspects.

23. Bottcher teaches of the production of neutral transition metal complexes in a one-step process wherein the complexes are prepared via microwave irradiation of metal ions and multitoothed chelating ligands (i.e. dioxime (N and O containing) in an aqueous medium.

24. Griffiths et al. teaches that the method of producing a radiolabeled gallium complex involves reacting the solution (i.e. pH-neutral buffer) of a peptide labeled macrocyclic chelate with the ^{68}Ga diluted (dilute acid) from the $^{68}\text{Ge}/^{68}\text{Ga}$ titanium dioxide generator which can be fitted with an anion-exchange membrane. Therefore the reaction takes place in a solvent (i.e. aqueous) at 45°C for 30 minutes.

25. Therefore, it would have been obvious to one ordinarily skilled in the art to utilize the microwave technique of Bottcher and/or Lidström et al. for the method of Griffiths et al. for the advantage of minimizing the reaction time from 30 minutes to a few minutes as Bottcher teaches of the use of such as microwave technique for the preparation of neutral transition metal complexes via the reaction of metal ions and multitoothed chelating ligands in an aqueous medium.

Double Patenting

26. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3,5 and 8-15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1,2 and 6-14 of copending Application No. 10/522,206.

Claims 1-3,5,8-13 and 15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3,7-15 of copending Application No. 11/358,681.

Applicant asserts that they will file a suitable terminal disclaimer in the event that the instant application is deemed allowable.

Conclusion

27. No claims are allowed at this time.
28. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **MELISSA PERREIRA** whose telephone number is (571)272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

/Melissa Perreira/
Examiner, Art Unit 1618